REMARKS

Claims 1-35 are pending in the application.

Claims 28-33 and 35 have been amended. Independent claims 28 and 33 have been amended to recite Formula (I) and its accompanying definitions. Claims 29, 30, 31, and 32 have been amended to recite explicitly the limitations of claims 7, 13, 21, and 27, respectively. Finally, claim 35 has been amended to correct a typographical error. No new matter has been introduced by these amendments.

Claims 29-32 are objected to under 37 C.F.R. § 1.75(c) as being in improper form. This objection is rendered moot by the amendments to claims 28-32.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 33 and 34 are rejected under 35 U.S.C. § 112, first paragraph "because the specification, while being enabling for breast cancer, does not reasonably provide enablement for treating all types of cancers" (Action, page 2, part 4). To support the rejection, the Office relies on the relevant factors set forth in *In re Wands* 8 USPQ2d 1400 (CAFC, 1988) (Action, pages 2-4, part 4). According to the Action:

> In the instant case, the specification is not enabling based on at least four of the above mentioned eight factors such as quantity of experimentation necessary, the amount of direction or guidance provided, presence of working examples, the predictability or unpredictability and the breadth of the claims. ... It is also well known in the art that activity in vitro does not always correlate with in vivo activity. There are no working examples present showing efficacy of the instant compounds [*sic.* in] in vivo animal models of all types of cancers (Action, pages 2-3, part 4).

Applicants respectfully disagree.

Applicants' invention is based, in part, on the discovery that the claimed 9-anilinoacridine derivatives of formula (I) have, e.g., antitumor properties. As such, the claimed compounds can be useful for the treatment of cancer, e.g. "a human leukemia, sarcoma,

osteosarcoma, lymphoma, melanoma, ovarian, skin, testicular, gastric, pancreatic, renal, breast, prostate colorectal, head and neck, brain, esophageal, bladder, adrenal cortical, lung, bronchus, endometrial, cervical or hepatic cancer" (Specification, at page 5, lines 11-14).

The Specification teaches, for example, that the effects of the claimed compounds on inhibition of tumor cell growth were determined in "human tumor cells (i.e. colon HT-29, nasopharyngeal carcinoma HONE-1 and BM-1, hepatoma Hepa-G2, breast carcinoma MX-1, gastric carcinoma TSGH, brain tumor DBTRG, oral carcinoma KB, breast carcinoma MCF-7 and MX-1, and T-cell acute lymphocytic leukemia CCRF-CEM)" in a 72 hour incubation using the "XTT-tetrazolium assay described by Scudiero *et al.* (*Cancer Res.* **1988**, *48*, 4827-4833)" (Specification, Example 16, at page 18, lines 1-6). The Specification further discloses that compounds **1-6** were tested on five of the human tumor cell lines using this assay. Compounds **1-6** all exhibited IC_{50} values that were lower than those for known 9-anilinoacridine compounds in at least one of the five human tumor cell lines. In other words, according to the aforementioned assay, the instant compounds were superior to known 9-anilinoacridines in inhibiting tumor cell growth against one or more human tumor cell lines.

Applicants also note there is no requirement to conduct or submit clinical trial data or comparative test data. As pointed out in MPEP, 2107.02III, "[i]f reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process." Thus, if reasonably correlated to an asserted particular utility, suitable *in vitro* data or animal data are sufficient. It is well established that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlative to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing PTO decision based on finding that *in vitro* data did not support *in vivo* applications)." See MPEP 2164.02. The Office has stated, "that activity

in vitro does not always correlate with in vivo activity." However, as discussed above, the legal standard is reasonable correlation and not absolute correlation. Applicants submit that the disclosed test methods (as well as those known in the art) are reasonably correlative to cancers in a human being or in an animal and therefore meet the legal standards set forth in the relevant case law.

With regard to quantity of experimentation necessary, Applicants submit that some experimentation may be required to practice the invention, but not undue experimentation. It is held in *In re Colianni* and *In re Wands*:

> [A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance (In *In re Colianni*, 195 USPQ, 150, 153, (CCPA, 1977)).
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine (*In Re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) (emphases added).

The instant specification provides ample guidance and direction in the form of a roadmap of preferred compound attributes, exemplary compounds, and synthesis procedures along with art-recognized and routine test methods for evaluating inhibition of human tumor cell growth in culture, growth inhibition of CCRF-CEM human lymphoblastic leukemic cells and its drug-resistant sublines, and chemotherapeutic efficacy of compounds on the inhibition of nude mice bearing human breast tumor MX-1 xenograft. Further, the Specification provides a regimen and recommended dosages for administering the compounds to patients. Thus, a skilled artisan could make and use the claimed invention without undue experimentation, even though considerable.

The absence of a working example for "all types of cancer" involving man or animals is noted. According to MPEP 2164.02, "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." and "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." Applicants point out that while such a showing is not required and does not

automatically lead to a finding of lack of enablement, the presentation of an *in vivo* or *in vitro* animal model that "correlates" with a disclosed or claimed method can constitute a working example (see MPEP § 2164.02). As discussed above, Applicants have provided, for example, models that correlate with inhibition of growth of human tumor cells in more than one type of human tumor cell line. Thus, Applicants have presented working examples in the context of MPEP § 2164.02 that include cancers in addition to breast cancer.

Applicant would like to bring to the Examiner's attention that it is not necessary to test all species of formula (I) recited in claim 1 for treating any cancer. The law does not impose such a formidable burden on inventors seeking patent protection. "Appellants (here, Applicant) are **not** required to disclose every species encompassed by their claims even in an **unpredictable** art" (emphases added). *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976). In any event, Applicants have disclosed species, which provide varied and representative substitution patterns about both the aniline and acridine rings. Applicants submit that the exemplified compounds are commensurate in scope with the breadth of the instant claims.

A conclusion of lack of enablement means that based on the whole of the evidence regarding each of the undue experimentation factors, the specification at the time the application was filed would not have taught one of skill in the art how to make/use the invention without undue experimentation. As discussed above, Applicants' Specification provides ample guidance and direction as to how to make and use the claimed invention including, for example, assays based on art recognized *in vitro* models. There is no evidence that the amount of experimentation needed rises above the level of that routinely practiced in the drug discovery and medical arts. Applicants submit that the analysis of the factors weighs on the side of an enabling disclosure and respectfully requests that the rejection be withdrawn for the aforementioned reasons.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 28-35 are rejected as being indefinite.

According to the Action, claims 29-32 and 34 are indefinite because base claims 28 and 33, respectively, do not recite Formula (I). These rejections are moot in view of the amendments to claims 28-33.

According to the Action, claim 35 is indefinite because of the recitation of "formula (IV)" at "page 24, line 116." This rejection is rendered moot in view of the amendment to claim 35.

According to the Action, "the term---cancer--- is indefinite since specific type of cancer is not defined (Action, page 4, part 6).

Applicants respectfully disagree. According to the MPEP:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP § 2173.02).

As discussed above, the specification delineates various cancers that can be treated by administration of the claimed compounds (specification, e.g., at page 5, lines 11-14 and page 18, line 1 through page 19, line 22). Moreover, the term cancer is a well-established and understood term in the medical arts. Therefore, one of ordinary skill in the art reading Applicants' specification would understand the meaning of the term "cancer" in claim 33. A definite claim is a claim that apprises one of ordinary skill in the art of its scope and serves notice to others as to what constitutes infringement of the patent (MPEP 2173.02). Applicants thus submit that claim 33 is definite and meets the statutory requirements of 35 U.S.C. 112, second paragraph and respectfully request withdrawal of the rejection for the reasons set forth above.

Rejection under 35 U.S.C. § 102(b)

Claims 1-3, 8, 10, 13, 22, 28, 30, 33, and 34 are rejected as being anticipated by Denny et al., *J. Med. Chem.*, **1982**, *25*, 276-315 (Denny). According to the Action:

> Denny discloses potential antitumor agents. The compound no. 79 (see table 1 on page 279) disclosed by Denny anticipates the instant claims when R1 represents H, R4 represents CH3 and both m and n are 0 in the instant compounds of formula (I). It is of note that the applicants have put a proviso to exclude this compound. However, this proviso does not exclude this compound since even when R5 and R6 both are not hydrogen, both m and n can still be zero (Action, page 5, part 7, emphasis added).

Applicants respectfully disagree. Claim 1 recites the proviso: "when R^1 is hydrogen and R^4 is CH_3, R^5 and R^6 cannot both be hydrogen." The fact that variables R^5 and R^6 are positively recited in the body of the proviso means that when R^1 is hydrogen and R^4 is CH_3, then:

(i) R^5 and R^6 must both be present; and

(ii) at least one of R^5 and R^6 must have a value other than hydrogen.

When both m and n are zero, R^5 and R^6 vanish, and are therefore absent, from formula (I). Since the proviso requires that R^5 and R^6 must both be present when R^1 is hydrogen and R^4 is CH_3, then m and n cannot "still be 0" when R^1 is hydrogen and R^4 is CH_3 as asserted in the Action. Since m and n cannot be 0 when R^1 is hydrogen and R^4 is CH_3, then Applicants' proviso does in fact exclude Denny's compound number 79 from the instant claims. Denny therefore does not anticipate claims 1-3, 8, 10, 13, 22, 28, 30, 33, and 34. Applicants therefore respectfully request withdrawal of the rejection on the above grounds.

Publication date of Chang, *Bioorg. & Medicinal Chemistry*, vol. 11 (23), pages 4959-4969 (2003) (Chang).

According to the Action, the instant claims are anticipated by Chang. However, the Examiner indicated that the publication date of Chang was unavailable as of the mail date of the Action. Further to the Examiner's request, Applicants have verified the publication date of Chang. Applicants have received verbal confirmation from Shirley Goldsborough, Production Specialist at Elseiver Journals, that the November 17th issue of *Bioorg. & Medicinal Chemistry* (volume 11, number 23) was made available online on October 20, 2003 and as a printed publication on November 11, 2003. Applicants' filing date (July 30, 2003) and earliest effective

filing date (April 4, 2003) both antedate the online and printed publication dates of Chang. Therefore, Chang cannot be applied as a reference under 35 U.S.C. § 102 against the instant claims.

CONCLUSION

Applicants submit that all claims are in condition for allowance. No fee is believed due. Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 08919-094001.

Respectfully submitted,

Date: July 14, 2004

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